REMARKS

This Reply is responsive to the Office Action dated August 16, 2001. Entry of the foregoing and reconsideration on the merits pursuant to 37 CFR 1.116 is respectfully requested.

The application has been amended as set forth above. In accordance for the new rules for amending applications set forth in 37 CFR 1.121, which took effect on March 1, 2001, a clean copy of the pending claims is attached hereto as an appendix.

Claim 21 clarifies that the recited tissue culture medium is a complete medium that contains the four growth factors. Support for this amendment may be found on page 29, lines 9-15. Also the claims provide that claims 22-29 substantially correspond to previous claims 2-10 the method results in a culture comprising PGCs and EG cells.

New claims 30-32 correspond to previous claims 18-20, except that they expressly provide for the growth factors to be present.

Turning now to the Office Action, claims 9-10 and 20 stand rejected under 35 U.S.C. §112, first paragraph.

Particularly, the Examiner maintains that the specification does not enable transfecting or transforming EG cells. The basis for the rejection is that transfection of avian EG cells and the production of transgenic avians expressing an exogenous protein or having an altered phenotype were not known at the time the invention was made. However, contrary to the Office Action reply, the prior art had not failed in producing chimeric or transgenic avians, as evidenced by the Vick & Simkiss article submitted in the related application. (The Examiner indicated therein that the Vick & Simkiss article was not in the file, so a copy of the article is attached hereto for the Examiner's consideration).

Again, transgenic avians did exist prior to the present invention. Therefore, the goal of the present invention was not to produce a transgenic or chimeric avian per se as a novel invention. Rather, applicants' goal was to develop a long term culture system for avian PGCs that would *facilitate* the production of transgenic and chimeric avians, thereby making an already existing process easier. Furthermore, the ability to culture PGCs for prolonged periods not only facilitates the isolation of transfected PGCs, but also facilitates the isolation of transfected EG cells, because EG cell lines are produced as a result of long term culture of PGCs (see specification, page 6, lines 20-29). Facilitation of a transfected EG cell necessarily

follows facilitation of transfected PGCs, because transfected PGCs become transfected EG cells by the culturing process for which the present invention provides.

Thus, the Examiner has rejected claims directed to methods of making transgenic chimeric avians because of deficiencies in the prior art that do not exist. In this regard, the Federal Circuit has long held that 35 USC §112 does not require a specific teaching of that which is already known to one of ordinary skill in the art. Case v. CPC International, Inc., 221 USPQ 196, 201 (Fed. Cir. 1984). Moreover, the fact that applicants report that only 1 in 50 PGCs was transfected is not fatal, because the enablement test does not preclude all experimentation, just that which is undue.

As evidenced by Vick and Simkiss, persons of ordinary skill were not deterred from making transgenic chimeric avians even though they could not culture PGCs more than a few days, even though they could not confirm or select transfected PGCs before they proceeded with injection of the cells because they did not have a method for long term culturing, and even though they had to go through the entire process of hatching the chimeric birds and mating them to see if the transfection enabled germ line transmission. The fact that persons using prior art techniques still sought to make transgenic chimeric birds despite the fact that they did not have the benefit of applicants' culturing method suggests that, even in this uncertain environment, the level of experimentation was not undue.

Applicants fail to comprehend, then, how the presently claimed methods of making transgenic chimeric avians would require " undue" experimentation when the claimed methods only make the prior art methods easier, and the level of experimentation was not so inconceivably large to deter prior researchers from making transgenic chimeric birds in the absence of the benefits to be gained by applicants' invention. Indeed, as stated on page 181, column 2, of Vick and Simkiss, "clearly it is the number of primordial germ cells that can be obtained rather than their cellular maturity that determine[d] the success rate in forming these [transgenic] embryos. " Vick and Simkiss obtained a higher rate of success using primordial germ cells from the germinal crest before their vascular migration because more cells could be isolated; the present invention would have afforded them as many cells as needed. Moreover, the present invention would have permitted Vick and Simkiss to screen for transfected PGCs prior to chimera production, because the present invention allows for long term culturing of cells.

The Examiner dismissed in the related application the showing that PGCs may be transfected with a marker DNA as inadequate to overcome the " dearth" in the art regarding the production of transgenic avians expressing exogenous proteins and especially therapeutic proteins. However, it is not clear why expression of a marker gene such as GFP is not a sufficient means to demonstrate that expression of heterologous proteins in general is feasible in the cells and chimeric birds of the invention. Transfection of marker DNAs is the standard way to demonstrate transfection of a disclosed cell line, and to say that this is inadequate would be to call into question many issued patents.

Claims 1-10 and claims 18-20 were rejected under 35 U.S.C. §112, second paragraph. This rejection should be moot in view of the cancellation of claims 1-10 and 18-20 in favor of new claims 21-32.

Claims 1-8, 18 and 19 stand remain rejected under 35 U.S.C. §102(b) as being anticipated by Pain. Without agreeing with the rejection, applicants note that claim 1, the only independent rejected claim has been rewritten as new claim 21 to limit the invention to the use of a complete medium (i.e., one that contains calf serum and glutamine) that contains essentially the recited four growth factors. Therefore, the claim language is not open to the use of other growth factors, but would be open to other ingredients that are not essential. Pain does not anticipate the claimed methods because Pain teaches that ARMA is necessary and routinely used it in the culturing methods disclosed therein (see page 2342, col. 2, first paragraph). Therefore, the rejection is moot.

Notwithstanding the amendments made to expedite an allowance, applicants strongly disagree with the rejection and reserve the right to pursue broader claims in a continuation application. The Examiner refers to column 1 of page 2340 of Pain as providing support for the long term culturing of cells in the absence of a feeder layer. However, this is merely a general methodology section that describes how the culturing in the absence of a feeder layer was performed on a gelatin coated dish. It does not discuss the subsequent experiments was performed, nor does it teach that the absence of a feeder layer was combined with all the recited growth factors in a single method as claimed.

Indeed, the only place at which Pain describes actual experiments reporting the use of no feeder layer is in the testing of individual growth factors and combinations of growth factors that do not meet the limitations of the claim. In this regard, the examiner also refers to Figure 2B to support his arguments, but this figure only gives the results of culturing the cells

in the presence of individual growth factors and combinations of growth factors that do not meet the limitations of the claim. For instance, the closest combination tested is reported in Figure 2A, and included SCF, FGF, and LIF. But this does not meet all the limitations of the claimed invention. A reference cited under §102 must teach all the limitations of the claim.

Thus, even if Pain's five day "testing" period would be considered to be a prolonged period so as to meet the limitation of the claims, the relevant sections of Pain deal with the testing of individual growth factors and combinations of growth factors that do not anticipate the claimed methods. Indeed, the claimed methods require the absence of feeder cells and the presence of all the growth factors listed, simultaneously, in a single culturing method. The Examiner maintains, however, that without evidence to the contrary, all the "cultures" of Pain were maintained with or without a feeder layer, including the long term cultures (i.e., the cultures other than those maintained for testing growth factor combinations). However, the authors themselves state at page 2345, col. 2, lines 10-11, that long term cultures included a feeder layer. Applicants can think of no better evidence than the authors themselves stating that a feeder layer was present for the long term cultures.

Nevertheless, applicants have revised the new claimed methods such that they are all limited to the use of a complete medium containing essentially all the growth factors listed. Therefore, the claims would not encompass the use of IL-11 and ARMA as used in the cultures of Pain, therefore Pain is not an anticipatory reference. Applicants believe, however, that Pain does not anticipate the claims notwithstanding the amendment because Pain does not teach long term culturing in the presence of all the recited growth factors simultaneously in the absence of a feeder layer. Withdrawal of the rejection based on Pain is respectfully requested.

Claims 1-8, 18-19 also were rejected under 35 U.S.C. §103(a) as being allegedly unpatentable over Pain as evidenced by Simkiss. The rejection was maintained for the same reason that the 102 reference was maintained, i.e., because the Examiner believes that Pain teaches the use of the claimed combination of growth factors in the absence of feeder cells. However, as applicants discussed above, the claimed methods require the absence of feeder cells and the presence of all the growth factors listed, simultaneously, in a single long term culturing method. In contrast the authors of Pain state at page 2345, col. 2, lines 10-11, that their long term cultures included a feeder layer.

Nevertheless, applicants have cancelled claim 1 in favor of new claim 21 such that the claimed method is limited to the use of a complete medium containing essentially all the growth factors listed, and is no longer open to the inclusion of other cytokines or growth factors. Pain would not render obvious a method using a complete medium as defined by the recited four growth factors, because Pain teaches that ARMA, an antibody to retinoic acid, is necessary to neutralize endogenous retinoic acid (see discussion at page 2342, col. 2). Pain also uses IL-11, a member of the LIF family of cytokines (see page 2345, col. 1), maintain the ES-like properties of the cells. Further, both ARMA and IL-11 were included in the long term cultures (see page 2345, col. 2). Applicants believe, however, that Pain does not render obvious the claims notwithstanding the amendment because in contrast to what is alleged in the Office Action, Pain does not teach long term culturing in the presence of all the recited growth factors simultaneously in the absence of a feeder layer. Withdrawal of the §103(a) rejection based on Pain is respectfully requested.

Claims 1-8 and 18-19 remain rejected over claims 1-12 of U.S. Patent No. 6,156,569 alone or in view of Pain et. al. (Id.) for obviousness-type double patenting. A terminal disclaimer as to the remaining patent term not coextensive with the term of the of the '569 patent will be provided upon induction that this case is otherwise allowed.

All issues raised by the Office Action dated August 16, 2001 have been addressed in this Reply. Accordingly, a Notice of Allowance is next in order. Applicants have made substantial efforts to expedite an allowance in the present case, so if the Examiner has any further issues to raise regarding the subject application, it is respectfully requested that he contact the undersigned so that such issues may be addressed expeditiously.

Respectfully submitted,

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